liquid. This design may incorporate the hydrophobic/hydrophilic surface tensions described above to retain liquid between the cover slip and the substrate slide. The substrate slide is patterned so that the area that contains probes of interest, such as DNA probes, is hydrophilic, while the surrounding areas are hydrophobic.

[0141] In the absence of the cover slip, aqueous solution applied to the substrate slide will form a droplet on top of the hydrophilic area with a contact angle determined by the hydrophobicity of the surrounding area (shown in Side View **1**, **FIG. 10**). When a cover slip is positioned on top of the droplet, a smaller volume of liquid is required to fill the same-sized hydrophilic area (Side View **2**, **FIG. 10**). Due to the surface tension, the aqueous solution will be confined within the hydrophilic region, and the cover slip can be supported by the aqueous solution, thereby "floating" on top of the droplet.

[0142] The cover slip coupled with the microarray substrate forms an assembly which in some embodiments can be placed in a slide holder. The slide holder can serve to seal the assembly to inhibit evaporation and limit the movement of the substrate slide or the cover slip.

[0143] Various assembly designs can be used to generate relative motion between the cover and the substrate. In **FIG. 12**, an immobilized substrate slide (**2**) having a plurality of probe arrays (**4**) is confined by barriers (**7**) on the substrate holder (**1**) with relatively little room for movement. On the other hand, the cover slip (**5**) which floats on top the liquid sample is loosely retained by barriers (**8**) on the cover holder (**6**). Because the barriers (**8**) on the cover holder (**6**) provide some lateral clearance for the cover slip (**5**), the cover slip (**5**) can move laterally over a relatively larger area within the cover holder (**6**). A barcode (**3**) can be provided on the substrate slide (**2**) to facilitate handling and organization of the substrates.

[0144] The barriers (**8**) are engineered on the cover holder (**6**) so that when the entire assembly is agitated, the cover (**5**) will slide to one side until it hits the barrier (**8**). Agitating the assembly in multiple directions will result in the continuous movement of the cover slip, thus generating movement of the target liquid underneath. This sliding motion provides agitation to move the target molecules of the sample liquid to facilitate better binding with the probes in the microarray.

[0145] The barriers (**7**) and (**8**) can take various forms. In some embodiments, a single barrier encircles the entire substrate (**2**) or cover (**5**). In other embodiments, a plurality of smaller barriers are used to limit the movement of the substrate (**2**) or cover (**5**) in at least one direction.

[0146] In an alternative embodiment, the cover (**5**) can be immobilized in the cover holder (**6**). In this design, the cover (**5**), rather than the substrate (**2**), is confined by barriers on the cover holder (**6**). Confinement barriers in the substrate holder (**1**) will provide increased lateral clearance so that the substrate (**2**) will be able to move laterally for a limited distance.

[0147] In another embodiment, the cover slip may have protrusions or ridges to enhance the agitation of the target liquid and generate more effective movement of the target liquid underneath. For example, the protrusions can be formed as tooth-like ridges such as the design shown in **FIG. 11**.

[0148] In **FIG. 11**, the cover slip is fabricated to have tooth-like structures on the surface that contact the target liquid. Each of these teeth are formed as a ridge with a front side that is aligned roughly perpendicular to the surface of the substrate (a 90° angle) and a back side that is at less than a 90° angle to the substrate surface. Because of the shape of these teeth, the liquid is "pumped" to flow preferentially in one direction when the cover slip moves vertically up and down.

[0149] A small rocking motion can be introduced into the vibration to enhance the pumping action, as shown in **FIG. 11**. This can be achieved by attaching a PZT on the cover or placing the substrate/cover assembly on a vibration table designed for supporting the substrate while moving the cover slip. The cover slip is driven to move up and down against the substrate slide by an acceleration force generated by generated by the PZT or some other motion or vibration inducing device.

[0150] In some embodiments, the orientation of the ridges changes direction on opposite edges of the cover slip. In this way, a rotational flow pattern can be established when the cover slip is moved in a circulating motion relative to the microarray substrate slide, as shown in **FIG. 11** to generate a circular flow in the target liquid.

[0151] 3. Substrate

[0152] Hybridization can also be promoted by introducing active movement of a target liquid during hybridization by mechanically moving the microarray substrate or substrate slide. As illustrated in **FIG. 13**, instead of introducing target liquid onto a microarray substrate slide as in conventional hybridization devices, a microarray substrate slide (shown in **FIG. 13** as microarray carrier) can be inserted into a cover slip having a reservoir containing the target liquid. Lateral and rotational movement can be introduced to the microarray substrate slide to encourage interactions between the target liquid and probes. For example, the slide and/or cover slip can be mounted in movable stages that impart lateral and/or rotational movements.

[0153] In some embodiments, the size of the sample liquid container is slightly larger than that of the microarray substrate slide to minimize the volume of target fluid used to cover the entire surface of the microarray. In the embodiment shown in **FIG. 13**, the microarray substrate slide is not a standard microscope slide. Instead, the substrate is shown as a cylindrical microarray carrier having the probe microarray deposited on one end. In another embodiment, the microarray substrate slide is mounted to the facet of a rotating member, such as a short pole, and the sample solution is contained in the well of a standard microtiter plate. Multiple samples can be hybridized to multiple microarrays in parallel, but coupling multiple substrates with the multiple wells in the microtiter plate.

[0154] B. Fixed Substrate Slide and Cover Slip Hybridization Apparatus

[0155] An embodiment of a hybridization apparatus includes a cover slip formed with a very flat surface and with spacers provided on the outer edges of the slip. The height of the spacer can be precisely controlled using precision fabrication techniques, such as etching or electroplating. By forming the slip with an extremely flat surface and precisely-fabricated spacers, the thickness of the target fluid across the